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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,432	10/15/2001	Chen-Kun James Shen	08919-016003	3256
26161	7590	05/03/2004	EXAMINER KAUSHAL, SUMESH	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			ART UNIT 1636	PAPER NUMBER

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action**

Application No.

09/977,432

Applicant(s)

SHEN, CHEN-KUN JAMES

Examiner

Sumesh Kaushal Ph.D.

Art Unit

1636

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_

Claim(s) objected to: \_\_\_\_\_

Claim(s) rejected: 33-63.

Claim(s) withdrawn from consideration: \_\_\_\_\_

8. ☐ The drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_
10. ☐ Other: \_\_\_\_\_

  
JEFFREY FREDMAN  
PRIMARY EXAMINER

Continuation of 5. does NOT place the application in condition for allowance because

Claims 33-36, 41-46, 51-53 and 58-59 stand rejected under 35 U.S.C. 103(a), for the same reasons of record as set forth in the office action mailed on 12/23/03.

Applicant argues that the enhancer element may not function in a viral vector as suggested by McCune (*a reference cited by the applicant in support*). Therefore Zhang and Miller would have not motivated one to make a viral vector containing an enhancer in the way suggested by the combined teaching of prior art. Regarding McCune the applicant argues that the test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. The applicant argues that McCune relates to general problem of sustaining expression of retrovirus-transduced genes in primary tissues, therefore it is improper to consider only Zhang and Miller and disregard McCune. The applicant further argues that combined teaching of the cited art does not teach (1) a viral vector containing an enhancer, and (2) would not have motivated one skilled in the art to make such a viral vector, since McCune teaches that an enhancer does not function at all in a viral vector. The applicant concluded that invention as claimed is not obvious in view of cited prior art of record, especially in view of McCune (*a reference cited by the applicant in support*) who teaches an enhancer element (any) may not function in a viral vector.

However, this is found NOT persuasive because the response element as taught by McCune is not limited to the response element as claimed i.e. SEQ ID NO:1, therefore there is reasonable expectation of success that any response element other than as taught by McCune would be able function in any viral (retroviral) vector as claimed. The office recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. Zhang teaches an expression vector comprising, a tissue specific  $\zeta$ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). Zhang further teaches that mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (page 8502, col.2 para.6; page 8504 fig-3). Miller teaches the making of a N2 and LNL6 based retroviral vectors comprising a promoter operably linked to a gene of interest and a polyadenylation signal, wherein the high-titre retroviral vector has been used to transduce target cells (page 984, fig-3; page 986 table-3). Thus it would have been obvious to one ordinary skill in the art at the time of filing to make a retroviral vector as taught by Miller, wherein the promoter and gene of interest has been replaced with a nucleic acid sequences that encodes a tissue specific  $\zeta$ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone as taught by Zhang. One would have been motivated to do so because retroviral vectors has increased transfection efficiency as compared to plasmid base DNA transfection system. One would have reasonable expectation of success in doing so since making a retroviral vector encoding nucleic acid sequences of interest has been considered routine in the art at the time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claims 37-40, 47-50, 54-57 and 60-63 stand rejected under 35 U.S.C. 103(a), for the same reasons of record as set forth in the office action mailed on 12/23/03.

The applicant argues that Zhang and Miller do not suggest a viral vector containing an enhancer. The applicant argues that Jarman teaches a regulatory element of the human  $\alpha$  globin gene and does not teach or suggest making a viral vector containing a regulatory element, such as an enhancer. The applicant argues that Jarman does not rectify the common deficiencies of Zhang and Miller.

However, this is found NOT persuasive because Zhang clearly teaches that a mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer. Therefore, it would have been obvious introduce a point mutation (gctgagtca to tctgagtca) in the HS-40 enhancer region (Zhang) into the nucleotide sequences as taught by Jarman. Zhang clearly provide the motivation to make a single nucleotide change in order to enhance gene expression. Furthermore making a retroviral vector in view of Miller is obvious who teaches N2 and LNL6 based retroviral vectors comprising a promoter operably linked to a gene of interest and a polyadenylation signal, wherein the high-titre retroviral vector has been used to transduce target cells (page 984, fig-3; page 986 table-3). One would have a reasonable expectation of success, since making a point mutation and constructing a retroviral vector encoding the mutated nucleic acid sequences of interest has been considered routine in the art. Therefore considering the combined teaching of cited art (supra), the invention as claimed is prima facie obvious in view of cited prior art of record.